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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/035,324	BOSCH ET AL.	
	Examiner	Art Unit	
	MINA HAGHIGHATIAN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/20/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 13-37* is/are pending in the application.

4a) Of the above claim(s) *15-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-11, 13-14, 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/27/08 & 05/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments, Remarks and IDS filed on 05/20/08. No claims have been amended, cancelled or newly added. Claims 15-34 remain withdrawn. Accordingly, claims **1-7, 9-11, 13-14 and 35-37** remain under examination.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (5,747,001) in view of Desai et al (US 20070117862).

Wiedmann et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of insoluble **beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin, benzalkonium chloride, PVA, sorbitans, etc (see col. 3, line 30 to col. 4, line 45). A suitable surfactant is **tyloxapol** (see col. 4, lines 49-60), the particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see col. 6, lines 8-15 and col. 10, lines 25-35). The process of making such nanoparticles includes attrition and **filtration** (see col. 7, lines 18-21). It is disclosed that the concentration of the beclomethasone in the liquid medium can vary

from about 0.1 to 60%, and preferably from 5-30% (w/w) (see col. 6, lines 19-22). Wiedmann discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles (see col. 6, lines 23-28 and col. 10, lines 40-55). Wiedmann discloses filteration, but lacks teachings on sterile filtration.

Desai et al teach formulations for in vivo delivery of pharmacological agents in which the pharmacologically active agent is delivered in the form of suspended particles. There is also provided, a process of preparing unusually small **nanoparticles** of less than 200 nm in diameter, which can be **sterile-filtered**, through a 0.22 micron filter (see [0051]). Desai et al disclose methods for the preparation of substantially water insoluble pharmacologically active agents for in vivo delivery, said method comprising, combining an organic solvent having said active agent dissolved therein, water, a surfactant and a co-surfactant that spontaneously form a micro-emulsion and removing said organic solvent to yield a suspension of nanoparticles of said active agent in said water (see [0093] to [[0100]). It is further disclosed that insoluble active agents include inhalant corticosteroids such as beclomethasone dipropionate and budesonide (see [0122] and [0146]).

Examples **4, 5 and 8** disclose a nanoparticle formation wherein the dispersion is sterile filtered.

With regards to the new claim 35 recites the term "consisting of". Wiedmann teaches that the nanoparticles can be surface modified with any of the listed surface

modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see col. 3). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process claims. According to MPEP 2113 [R-1], product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai et al in the formulations and process of Wiedmann, since Wiedmann teaches filtration of nanoparticles of beclomethasone and tyloxapol. Thus, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wiedmann because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown

that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Weidmann teaches the formulations.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al (WO 9625918) in view of Desai et al (US 20070117862).

Wood et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of insoluble **beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin, benzalkonium chloride, PVA, sorbitans, etc (see pages 6-7). A suitable surfactant is **tyloxapol** (see page 8), the particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see page 16). The process of making such nanoparticles includes attrition and **filtration.** It is disclosed that the concentration of the beclomethasone in the liquid medium can vary from about 0.1 to 60%, and preferably from 5-30% (w/w) (see examples). Wood et al discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles. Wood et al discloses filteration, but lacks teachings on sterile filtration.

Desai et al, discussed above, teaches sterile filteration of dispersions of nanoparticles.

With regards to the new claim 35 recites the term "consisting of". Wood et al teaches that the nanoparticles can be surface modified with any of the listed surface modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see cols. 4-5). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process claims. According to MPEP 2113 [R-1], product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai et al in the formulations and process of Wood et al, since Wood et al teach filtration of nanoparticles of beclomethasone and tyloxapol. In other words, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wood because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique

for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Wood et al teaches the formulations.

Response to Arguments

Applicant's arguments filed 05/20/08 have been fully considered but they are not persuasive.

With regard to the rejection of claims over Wiedmann and Desai, Applicant argues that "Examiner overreaches in forming the conclusion from the teaching of Desai that its sterile filtration of all solid dispersions of nanoparticles in liquid medium is known in the art", and that "Examiner has ignored the unpredictability of successfully sterile-filtering solid dispersions of nanoparticles in liquid mediums as shown in the Examples of Applicant's original specification". In support of the first argument, Applicant states that paragraph [0167], which Examiner had pointed to in the previous Office Action, "states that the ability of sterile filter a composition having protein-rich particles is of great importance because one cannot sterilize such protein-rich particles by autoclaving". However, the above arguments are not persuasive because Desai meets all the limitations it is relied upon for and is not a teaching away from the claimed invention. It is considered that Wiedmann et al teaches the nanoparticles of budesonide and/or beclomethasone, surface modified by suitable modifiers and stabilizers such as tyloxapol in a dispersion for inhalation. All is missing from Wiedmann et al is sterile

filteration. Desai teaches dispersions of nanoparticles that are stabilized using stabilizers such as proteins (see abstract). Desai teaches that particles that are of unusually small size, i.e. less than 200 nm in diameter, can be sterile filtered through a 0.22 micron filter. It also states that this method in contrast to other methods such as autoclaving are specially suitable for protein containing particles because proteins can not be autoclaved. However this statement is not interpreted (by the Office) as meaning that Desai teaches that only protein rich particles can be sterile filtered. Desai also teaches that other surfactants and stabilizing agents are added to the particles. On the other hand, instant claims require a secondary stabilizing agent added to the particles, which may be a protein (see claims 1 and 9). Thus the combination of Wiedmann et al and Desai et al references would lead one of ordinary skill in the art to the instant claims. Examples 8 and 9 and others (such as 4 and 5 mentioned on the last paper) all while using a different active agent than budesonide or beclomethasone, disclose that if particles less than 200 nm in diameter are formed, they were sterile filtered through a 0.22 micron filter. Thus it is concluded that Desai provides adequate teachings to one of ordinary skill in the art having the nanoparticle dispersions of Wiedmann to sterile filter the particles by passing them through a 0.22 micron filter.

Furthermore, Desai et al teach that nanoparticles of active agents with surfactant and co-surfactants can be produced (see [0094] to [0100]). Suitable surfactants include nonionic surfactants such as Tween™, Span, Triton, Pluronic, etc, and anionic, cationic and zwitterionic surfactants (see [0271] and [0295]).

Applicant states that "Examiner ignores Applicants' evidence of unpredictability". (see page 13 of Remarks. This is not correct or persuasive. The Examples Applicant is referring to, Examples 1-18 of the specification have been considered by the Examiner in previous Office Actions (see e.g. Final Office Action mailed on 12/06/06, page 6). All examples have been considered and they show that if the particles have a diameter of larger than 200 nm, sterile filteration could not be performed. Those dispersions that contained particles with less than 200 nm in diameter, were successfully filtered. The only exception was Example 15, which is not clear why was not filtered even though the particle size was less than 200 nm. However, one unexplainable set of data is not support for unpredictability (1 out of 18). Applicant states that "Examples 13 had an effective average particle size of less than 0.2 micron, but was not successfully sterilized" (see page 15 of remarks). However, Examples 1-4 and 10-11 all harvested particles that had an average particles size of less than 200 nm and were filtered through a 0.22 micron filter. On the other hand Examples 5-9, 12-14 and 16-18 all harvested particles that were either too large or were highly aggregated and could not be filetered through a 0.22 micron filter. In fact, Example 13, reads "the dispersion was significantly aggregated. **Because** of the large average particle size of the nanoparticulate beclomethasone dispersion and its degree of agglomeration, the material **was unsuitable** for 0.2 micron sterile filteration". Therefore, Examples 1-18 support predictability, and Applicant's findings correspond to what would have been expected from a combination of prior art references on record.

Thus despite Applicants claim of unpredictability, there is no evidence of unpredictability and it is maintained that the combination of Wiedmann and Desai render instant claims obvious.

Applicant also states that "because the Examiner has advanced no contravening evidence or compelling logic to support the proposition that any nanoparticulate beclomethasone/budesonide compositions comprising particles having an effective average particle size of less than 150 nm would have been able to pass through a filter with pore size of 0.2 micron or less, the claimed invention is non-obvious over the cited art" (see page 16 of Remarks). This is not persuasive because Examiner has clearly shown evidence and a compelling logic to support the proposition that generally particles that remain in a particle size range of less than 200 nm can be sterile filtered through a 0.22 micron filter. As stated before, Desai is stating, as a general teaching, that the particle size determines whether particles can be passed through a 0.22 micron filter. Further evidence is seen in Patent 6,139,870 (to Verrecchia), provided by Applicant in the IDS filed on 02/27/08. Verrecchia discloses that "It has now been found, and this forms the subject of the present invention, that particles can be prepared, 95% of which have an average diameter of less than 100 nm, and more specifically have an average diameter of between 20 and 75 nm, and which can thus be subjected to a sterile filtration on 0.22 μm filters without a loss in yield. These particles are moreover more stable than those which could be obtained according to the prior art and can be lyophilized without leading to any phenomenon of particle agglomeration".

With regard to the combination of Wood and Desai, Applicant's arguments are the same as those made with regard to Wiedmann and Desai. The response then would be the same.

Applicant argues against the combination of Wiedmann and Westesen and requests withdrawal of this rejection. This argument is moot since this rejection was withdrawn in the Final Office Action mailed on 10/22/07.

In summary, the scope of instant claims is within the scope of the combined references because even if Desai's disclosure was different from the instant claims, the formulations are taught by Wiedmann and Wood et al, Desai was brought in and relied upon for the teachings of sterile filteration of dispersions of nanoparticles. It is disclosed and known in the art that sterile filters have a pore size of 0.2 micron. In order for any dispersions to go through the said filters, the particle size has to be at or less than 0.2 microns.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616